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St. John's Wort Reduces Digoxin Levels

ABSTRACT & COMMENTARY

Synopsis: *With the current increase in popularity of alternative, over-the-counter medications (particularly herbal "remedies"), clinicians should be aware of patients taking such products as well as the possible interactions between the products and prescription medications.*

Source: Johne A, et al. *Clin Pharmacol Ther* 1999;66:338-345.

Due to the increasing popularity of alternative or natural treatments, St. John's wort (*Hypericum perforatum*) has become widely used in the treatment of depression. Despite being largely available as an over-the-counter drug, very little is known about the pharmacokinetics of its ingredients and/or its drug interactions. With a single-blind, placebo-controlled parallel design, Johne and colleagues studied the interaction between hypericum extract LI160 (the putative active ingredient in St. John's wort) and digoxin. The LI160 preparation contained 92 mcg of hypericin per 300-mg tablet of dried hypericum extract.

All subjects, who were instructed not to smoke or consume alcohol, coffee, tea, cola beverages, or drugs, received a loading dose of digoxin 0.25 mg twice daily for two days then once daily thereafter. After the achievement of steady state for digoxin on day five, healthy volunteers who were 22-33 years of age received digoxin (0.25 mg/d) either with placebo (n = 12) or with 900 mg/d LI160 (n = 13) for another 10 days. Digoxin concentration profiles on day five were compared with day six (single-dose interaction) and day 15 (10th day of comedication).

The effect of a single dose of hypericum extract on digoxin kinetics did not achieve statistical significance, although the digoxin levels were slightly higher than the placebo group. After 10 days of comedication, trough levels of digoxin were reduced by ~33% in the hypericum group. Maximum levels (Cmax) and

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the area under the curve of digoxin were similarly affected (reductions of 28% and 26%, respectively). These parameters were also significantly lower compared to those for the placebo arm. Cotreatment with hypericum did not affect the elimination half-life of digoxin, suggesting that mechanism other than hepatic enzyme induction. The effect on digoxin seemed to be time dependent (maximum reduction not present until the 10th day). This fact, combined with the fact that the single-dose effect of hypericum co-administration did not reduce but rather raised digoxin levels, suggests that the mechanism was not due to an impairment of absorption by physicochemical binding of digoxin and hypericum in the gut.

COMMENT BY MICHAEL F. BARBER, PharmD

The current study is important for several reasons. First, the reduction of digoxin concentrations by hypericum is clinically significant since patients may lose efficacy of digoxin when St. John's wort (SJW) is taken concomitantly. Patients who claim that they have been adherent to their digoxin regimen may present with lower serum digoxin concentrations despite the fact that their dosage has not been changed. Alternatively, patients who have achieved therapeutic levels of digoxin while taking SJW may develop digoxin toxicity once they discontinue SJW.

Another important point about this finding is that this pharmacokinetic study illustrates the importance of studying both the acute and chronic effects of drug interactions. The acute effect of this combination, although not statistically significant, may have suggested to clinicians that SJW may raise serum digoxin levels, whereas the chronic administration showed an impressive reduction in serum digoxin levels. The findings of this study also suggest that SJW does not induce hepatic metabolism of digoxin. Marangell[1] has previously discussed that SJW is an inducer of CYP3A4, and can lower serum levels of substrates of that enzyme. However, hepatic metabolism of digoxin constitutes a relatively minor pathway. A large portion of digoxin metabolism takes place in the intestine. The intestinal degradation of digoxin may be mediated by P-glycoprotein, a product of the multiple-drug-resistance gene MDR1, which transports digoxin into the gut from the blood. Thus, the mechanism by which SJW reduces serum digoxin levels may be via induction of the P-glycoprotein transporter. This is consistent with several other CYP3A4-inducing drugs, such as rifampicin, which also induce the expression of P-glycoprotein.

Finally, the current study is yet another example of a drug interaction involving a nonprescription product. With the current increase in popularity of alternative, over-the-counter medications (particularly herbal "remedies"), clinicians should be aware of patients taking such products as well as the possible interactions between the products and prescription medications. (*Dr. Barber is Assistant Professor of Clinical Sciences and Administration, University of Houston College of Pharmacy, Houston, Texas.*) ❖

Reference

1. Marangell LB. *Psychiatric Medicine in Primary Care* 1999;1(3):17-18.

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A Rising PSA Does Not Predict Overall Survival After Radical Prostatectomy for Localized Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: *At 10 years, patients with a PSA recurrence after radical prostatectomy for localized disease have an excellent overall survival equivalent to those without a detectable PSA.*

Source: Jhaveri FM, et al. *Urology* 1999;54:884-890.

The objective of this study was to compare the overall survival in men with biochemical failure (bF) to those with no bF after radical prostatectomy for localized prostate cancer.

Radical prostatectomy was performed in 1132 consecutive patients between June 1986 and September 1998 and bF (prostate specific antigen [PSA] ≥ 0.2 ng/mL) with a mean follow-up of 56 months (range, 1-125). A total of 99 patients were treated with androgen ablation, and/or radiation) was documented in 213 patients (19%), with a mean follow-up therapy at the time of bF. Kaplan-Meier estimates of bF, metastasis-free survival, and overall survival were generated and compared.

The 10-year overall survival rates for patients with bF (88%) vs. patients with no bF (93%) were similar (P = 0.94). The survival rates of patients with bF were not statistically different than those of patients without bF when compared by age older than 65 years, preoperative PSA greater than 10 ng/mL, biopsy or specimen Gleason score of 7 or greater, clinical stage T2b-3, presence of extracapsular extension, positive surgical margins, and seminal vesicle invasion. Patients who received second-line treatment also had a similar 10-year survival rate (86%, P = 0.97). For 213 patients with bF, the metastasis-free survival rate at 10 years was 74%. The overall survival rate for patients with distant metastasis (56%) was markedly lower than those without distant metastasis. Jhaveri and colleagues conclude that at 10 years, patients with a PSA recurrence after radical prostatectomy for localized disease have an excellent overall survival equivalent to those without a detectable PSA. Within this period, the clinical significance of a detectable PSA needs to be further evaluated.

COMMENT BY RALPH R. HALL, MD, FACP

I have recently given a lot of thought to PSAs. I received a physical examination on an afternoon following some intense interval running. My PSA drawn that afternoon was 6 ng/mL. I was assured that exercise would not alter my PSA results. However, I asked for a repeat and for a percent-free PSA to be determined. The repeat PSA was 4.6 ng/mL and the percent-free PSA was 15%. Approximately one year earlier, my PSA had been 4 ng/mL, so I reasoned that my PSA velocity was less than 0.75 ng/mL per year and might not be so bad.

The percent-PSA of 15% seemed to convince everyone that I had prostate cancer. A look at a recent report on age-related PSA and percent-free PSA reduced my concern, however. In the report by Kalish and McKinlay involving 983 men (96% white), it was demonstrated that the percent-PSA does not change with age.[1] The 50th and fifth percentiles of percent-PSA in their study were 25.3% and 13.2%, respectively. Thus, a PSA of 15% was not necessarily diagnostic of cancer. My biopsy was negative for prostate cancer.

As PSA determinations are refined and more data regarding age, race, and initial levels of free PSA are accumulated, we should develop better prognostic specificity and sensitivity for these tests. In the meantime, they are helpful guides, but a thorough rectal examination is still a useful test. ❖

Reference

1. Kalish LA, McKinlay JB. *Urology* 1999;54:1022-1027.

Dilated Coronopathy?

ABSTRACT & COMMENTARY

Synopsis: *Dilated coronopathy is characterized by nonobstructive coronary artery flow reductions and myocardial ischemia. Also, nitroglycerin is of no therapeutic benefit.*

Source: Kruger D, et al. *J Am Coll Cardiol* 1999;34: 1461-1470.

An occasional patient with exertional angina or myocardial infarction (MI) will have coronary artery ectasia or aneurysm (CEA) formation on coronary angiography without significant stenosis. Why do these patients have myocardial ischemia is the question asked by Kruger and colleagues. Among 16,341 patients undergoing cardiac catheterization between 1986 and 1997 in two university hospitals in Germany, 507 with CEA were identified (3%). Saccular aneurysms were found in 14,

unilateral fusiform aneurysms in 39, and 387 had CEA with significant coronary stenoses. These 440 patients were excluded, leaving the study population of 67 patients with bilateral fusiform CEA without significant stenoses or dilated coronopathy. Of the 67 patients, 25 had MI and 11 of these had occlusion of the infarct-related artery. Further studies were done on the 42 patients without prior infarction. Typical exertional angina was present in 37 of these 42, and five had atypical symptoms severe enough to warrant catheterization. Pacing stress coronary sinus lactate studies documented myocardial ischemia in 32 of the 42 patients (reduced lactate extraction), and exercise ECG testing was positive for ischemia in 29. These results were markedly different from a control group of 29 patients with a similar risk profile but no heart disease. Nitroglycerin markedly accentuated the ischemic response to pacing with 32 of 42 patients developing lactate production. Coronary artery luminal diameters were strongly related to the severity and extent of ischemia ($r = 0.87$; $P < 0.001$) and stigmata of impaired coronary blood flow, such as delayed antegrade filling, segmental back flow, and local dye deposition ($P < 0.04$). Kruger et al conclude that dilated coronopathy is characterized by nonobstructive coronary artery flow reductions and myocardial ischemia. Also, nitroglycerin is of no therapeutic benefit in this entity.

COMMENT BY MICHAEL H. CRAWFORD, MD

The angiographic literature suggests an incidence of CEA ranging from 0.3-4.9%, so the 3% incidence in this study is believable and agrees with my experience. This study clearly showed that CEA without significant stenoses can be a cause of myocardial ischemia (about 75% incidence in this study). Also, this study shows that MI can occur in patients with CEA (33% incidence in this study). In addition, Kruger et al demonstrated that exercise-induced ischemia can be found in the majority of symptomatic patients with nonobstructive CEA. Finally, Kruger et al showed evidence of reduced coronary blood flow in nonobstructive CEA patients with symptoms. Thus, the clinical presentation of nonobstructive CEA is similar to garden variety coronary atherosclerosis and this specific diagnosis must be made with coronary artery imaging or direct inspection.

The etiology of CEA is not completely clear. Perhaps half the cases or more are associated with atherosclerosis, 20-30% may be congenital, and 10-20% are of inflammatory origin (vasculitis). In this series of middle-aged adults (mean age, 53 years) without evidence of inflammatory diseases, most probably had coronary atherosclerosis. Why do some patients with atherosclerosis develop CEA? This answer is unknown, but some theories have been advanced. One is that CEA represents post-stenotic dilatation. This could be, but doesn't explain the frequent occurrence of prestenotic lesions. Histologic studies show an increase in the intimal layer with thinning of the media in atherosclerotic cases and loss of media in nonatherosclerotic cases, suggesting that loss of the media is a common pathway to CEA. Why some patients with atherosclerosis lose media and develop CEA is unknown, but could be genetic. Also, some have suggested that this is a compensatory mechanism to try to open the lumen of the vessel.

The mechanism of myocardial ischemia in nonobstructive CEA is also unclear. The reduction in epicardial coronary artery blood flow observed could simply be a result of vessel dilatation by Poiseuille's law or may be due to impaired microvascular flow. The latter could be caused by microemboli from the aneurysmal areas. Thus, our usual armamentarium for coronary disease is largely appropriate for these patients. Unstable angina and MI should be treated in the usual way with the caveat that IV nitroglycerin may be ineffective or even harmful. In the chronic patient, platelet inhibition seems particularly important, but the role of warfarin is unclear. Some would argue that chronic warfarin could be important to reduce microemboli or frank coronary occlusion due to flow stasis in these aneurysmal vessels, but there is no evidence to support its use or nonuse. Beta-blocker therapy seems reasonable, especially in symptomatic patients since this study showed pacing-induced ischemia. However, since nitrates were ineffective, what about calcium blockers? They also dilate coronary arteries and could be as ineffective as nitrates, but there are no data on this topic. In general, therapy of patients with dilated coronaropathy should be individualized to the particular situation with attention to the issue that coronary vasodilatating drugs may not be effective. (*Dr. Crawford is Robert S. Flinn Professor, Chief of Cardiology, University of New Mexico, Albuquerque.*) ❖

Hysterectomy and Sexuality

ABSTRACT & COMMENTARIES

Synopsis: *In a prospective study, all sexual functioning improved after hysterectomy.*

Source: Rhodes JC, et al. *JAMA* 1999;282:1934-1941.

Rhodes and associates from the university of Maryland performed a two-year, prospective

study of hysterectomy. This, the Maryland Women's Health Study, began with 1299 patients scheduled to undergo hysterectomy and concluded with 1101 women providing information about their functioning at six, 12, 18, and 24 months after a hysterectomy performed in 1992 or 1993. Bilateral removal of the ovaries was documented in 43.7% of the patients. Frequency of sexual relations increased after hysterectomy and the percentage of patients who had not been sexually active decreased. These changes were statistically significant, comparing post-hysterectomy to pre-hysterectomy behavior. An impressive change in dyspareunia occurred, decreasing from 40.8% to 14.9% two years after hysterectomy. Two-thirds of the women not experiencing orgasms prior to hysterectomy were having orgasms one year after surgery. Another striking feature involved libido, defined as frequency of sexual desire. More than 70% of the women with low libido before hysterectomy reported an improvement postoperatively. Approximately 30% of the participants were not sexually active just prior to hysterectomy, and of those 325 women, 45.5% were sexually active for two years after surgery. Rhodes et al conclude that overall hysterectomy was associated with an improvement in sexual functioning.

COMMENT BY LEON SPEROFF, MD

The idea that hysterectomy adversely affects sexual functioning is a common anxiety among our patients and has been intermittently promoted in the medical literature. Women who undergo hysterectomy experience an overall improvement in their health and quality of life. Therefore, it is not surprising that sexual functioning reflects this overall improvement. It is also commonly observed that hysterectomy frees the patient from vaginal bleeding and the fear of pregnancy. The study is noteworthy in documenting an improvement in quantity- and quality of life. Many writers have postulated that hysterectomy could affect orgasm, either through scar tissue or the elimination of tissue providing sensory response. In my view, the documentation of improved frequency and strength of orgasms is one of the most valuable contributions of this report. Many of the women who reported vaginal dryness prior to hysterectomy were no longer experiencing it after surgery. This improvement was present even when Rhodes et al adjusted for the post-hysterecomy use of hormone therapy. However, this adjustment was confounded by the fact that 88% of the premenopausal women who underwent bilateral oophorectomy were using hormonal therapy. It is likely that the postoperative use of hormone therapy was a major factor in the problem of vaginal dryness.

COMMENT BY SARAH L. BERGA, MD

The much-neglected topic of women's sexuality is now receiving needed investigative attention. I am happy to have the opportunity to bring this meticulously done study from the *Journal of the American Medical Association* to your attention. The current study clearly demonstrates that when the gynecologic condition to be relieved is benign and associated with symptoms that interfere with sexual functioning, hysterectomy is not likely to further impair sexual functioning. In fact, improved sexuality is likely in these circumstances. While not all women contemplating hysterectomy may ask about the effect of the procedure upon sexual functioning, they most certainly think about it. When three prospective studies concur, reassurance is in order. Obviously, it is better for the physician to bring this to the patient's attention rather than waiting to be asked.

It is often held that the quality-of-life parameters cannot be validly assessed in a clinical investigation. This study clearly demonstrates that such nihilism is unwarranted. The importance of including quality-of-life measures is gaining ground. Validated assessment tools are available, and the expertise for developing and implementing such tools is not as rare as in the past. Therefore, there is really no excuse for not foraying into this arena when attempting to understand the effect of clinical therapies, be they procedures or pharmaceuticals. Quality-of-life information is critical and does much to clarify, guide, reassure, and dispel myths. (*Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland; and Dr. Berga is Associate Professor, Departments of Obstetrics, Gynecology, Reproductive Sciences, and Psychiatry, University of Pittsburgh.*) ❖

Pharmacology Update

Moxifloxacin Tablets (Avelox - Bayer)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

In december 1999, the fda approved moxifloxacin, a new, once-daily quinolone for the treatment of respiratory tract infections. The new antibacterial agent will be marketed by the Bayer Corporation as Avelox. Moxifloxacin is a 8-methoxyfluoroquinolone with antibacterial activity against gram-positive, gram-

negative, and anaerobic bacteria with good activity against common respiratory pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Moraxella catarrhalis.*

Indications

Moxifloxacin is approved for the treatment of adults (≥ 18 years of age) with the following infections caused by susceptible strains of microorganisms:[1] acute bacterial sinusitis caused by *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*; acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, or *M. catarrhalis*; community-acquired pneumonia (mild to moderate severity) caused by *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, or *M. catarrhalis*.

Dosage

The recommended dose is 400 mg once daily. The duration is five days for acute bacterial exacerbation of chronic bronchitis and 10 days for acute bacterial sinusitis and community-acquired pneumoniae. The tablets may be taken with a liberal amount of fluid without regard to meals. The dose should be taken at least four hours before or eight hours after antacids (magnesium or aluminum based), sucralfate, didanosine buffered tablets or pediatric powder, and metal cations such as iron and zinc, including multivitamins.[1]

Dosage adjustment is not necessary in patients with renal insufficiency. However, moxifloxacin is not recommended in patients with moderate or severe hepatic insufficiency.[1]

Potential Advantages

In vitro data suggest that moxifloxacin is more active than sparfloxacin, levofloxacin, and ofloxacin against *S. pneumoniae* with intermediate resistance to penicillin.[2] These isolates were selected from blood cultures of patients with pneumococcal pneumonia. The MIC90 (0.25 mg/L) was one dilution lower than sparfloxacin, three dilutions lower than levofloxacin, and four dilutions slower than ofloxacin. As with other fluoroquinolones, moxifloxacin achieves good tissue levels. Concentrations three hours post-dose in respiratory tissue (e.g., bronchial mucosa, epithelial lining, alveolar macrophages) and sinus mucosa average at least 1.7 (range, 1.7-21.1) times that of plasma concentrations.[1] Gram-positive microorganisms resistant to other fluoroquinolones may be susceptible to moxifloxacin.[1] Moxifloxacin is approved for a five-day course for the acute exacerbation of chronic bronchitis compared to 7-10 days for other regimens.

Potential Disadvantages

Moxifloxacin has been reported to prolong the QT interval. The effect may increase with increasing concentration.[1] In clinical trials, the mean prolongation of QTc was 6 ± 26 msec. The drug should be avoided in patients receiving Class 1A or III antiarrhythmics, patients with proarrhythmic conditions, or patients taking drugs which can prolong QT intervals (e.g., erythromycin, cisapride).

Common side effects related to moxifloxacin include nausea (8%), diarrhea (6%), dizziness (3%), and headache, abdominal pain, and vomiting each at 2%.[1]

Comments

Moxifloxacin is a new 8-methoxyfluoroquinolone with a broad spectrum of activity including gram-negative and gram-positive anaerobes.[4,5] It is particularly effective against common respiratory pathogens including resistant *S. pneumoniae*. The efficacy and safety of moxifloxacin in these infections were based on several randomized, controlled, double-blind, comparative trials. Moxifloxacin (400 mg daily for 5 days) was compared to clarithromycin (500 mg twice daily for 10 days) for the treatment of acute bacterial exacerbation of chronic bronchitis and (400 mg daily for 10 days) in clinically and radiologically documented community-acquired pneumonia.[1] In the chronic bronchitis trial, clinical success was comparable at 7-17 days post-therapy, 89% (n = 501). Similar results were reported for community pneumonia, 95% clinical success for moxifloxacin and clarithromycin (n = 382), and 89% for moxifloxacin compared to amoxicillin (1 g three times daily) (n = 362).[1,5] In a multinational study (n = 649), moxifloxacin (400 mg for 5 days) was comparable to clarithromycin (500 mg for 7 days) in acute exacerbation of chronic bronchitis, although bacteriological success favored moxifloxacin.[3] However, bacteriological success was assessed in only 35% of the clinically evaluable patients. In the treatment of acute bacterial sinusitis, moxifloxacin (400 mg for 10 days) and cefuroxime axetil (250 mg twice daily for 10 days) were found to be comparable in clinical cure assessed 7-14 days post-therapy, 90% vs. 89%.[6]

Moxifloxacin is priced at $44 for a five-day course or $87 for a 10-day course.

Clinical Implications

Several new quinolones have been introduced to the

market as "ideal agents" to treat various respiratory tract infections with particular focus activity against drug-resistant *S. pneumoniae*. Moxifloxacin is the fifth quinolone to be approved for treating various respiratory tract infections (others being levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin, with gatifloxacin to follow). None of the older agents has emerged as the "ideal agent." Sparfloxacin has been associated with photosensitivity and prolongation of QT intervals. Glaxo Wellcome has voluntarily withdrawn grepafloxacin from the market due to increased risk of torsade de pointes. The FDA has issued a health advisory to physicians concerning the risk of severe liver toxicity due to trovafloxacin. Levofloxacin, which may be less active against *S. pneumoniae*, is not associated with these toxicities and is recommended by some experts as a good choice for older patients with underlying disease.[9] Moxifloxacin carries the potential to prolong QT intervals, which will bear close watching.

Fluoroquinolones should be prescribed prudently. They should not be prescribed for respiratory syndromes when an antibiotic is not appropriate or in infections where other classes of antibiotics are more appropriate. The increased prevalence of *S. pneumoniae* with reduced susceptibility to fluoroquinolones has been seen in Canada as well as in other countries.[7,8] ❖

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CME Questions

3. Which of the following is true?
- a. St. John's wort, taken in conjunction with digoxin, may result in the reduction of digoxin concentrations.
- b. St. John's wort, taken in conjunction with digoxin, may result in reduced efficacy of digoxin.
- c. Patients who have achieved therapeutic levels of digoxin while taking St. John's wort may develop digoxin toxicity once they discontinue St. John's wort.
- d. All of the above

4. The following statements are true of hysterectomy and sexual functioning *except*:
- a. There is no evidence that any specific surgical approach for hysterectomy has a better or worse outcome in terms of subsequent sexual functioning.
- b. Overall, the surgical removal of an unhealthy uterus improves general health and sexuality.
- c. The uterine cervix is an essential element in the physiology of an orgasm.
- d. Psychological morbidity prior to hysterectomy is associated with continuing problems, including decreased libido after hysterectomy.

5. Which one of the following statements is *not* true?
- a. PSA velocity of less than 0.75 ng/mL is not likely to indicate the presence of prostate cancer.
- b. The percent-free PSA does not change with age.
- c. 50% of men have percent-free PSAs of less than 25.3%
- d. The overall survival rate in patients with distance metastasis is the same as those with local extension of prostate cancer.

6. Which of the following is not an FDA approved indication for the use of moxifloxacin?
- a. Acute bacterial sinusitis
- b. Pharyngitis and tonsillitis
- c. Acute bacterial exacerbation of chronic bronchitis
- d. Mild to moderately severe community-acquired pneumonia

7. Which of the following is *not* true of moxifloxacin?
- a. is dosed once daily
- b. has good penetration into respiratory tissue
- c. does not increase QT interval
- d. is active against common respiratory pathogens

8. Coronary ectasia and aneurysms are associated with:
- a. myocardial ischemia.
- b. Marfan syndrome.
- c. hereditary telangectasia.
- d. None of the above

By Louis Kuritzky, MD

Continuing Screening Mammography in Women Aged 70-79 Years

There has been no prospective, randomized, controlled trial that proves benefit for screening mammography (SM) in women older than age 70. In fact, pooled data from women older than 70 who had undergone SM in Sweden showed no reduction in breast cancer mortality. Numerous factors affect women of this age group, which have bearing upon trial analysis: 1) older women have a shorter life expectancy, reducing screening benefits; 2) women with low bone mineral density (BMD) have a demonstrated lower incidence of breast cancer, and this favorable proclivity can be easily determined; 3) ductal carcinoma in situ (DCIS) increases with age and among screened populations, but it does not appear to affect overall mortality; 4) it appears likely that older women will place higher value on present health status than future health status, which likely affects their therapeutic decision processes.

To address such issues, Kerlikowske and colleagues used a decision analysis comparing women who continue screening after age 69 vs. those who do not based upon a lower bone mineral density obtained at age 65.

The screening of all women until age 79 years was found to save 0.3 days of life per woman, compared with a strategy of checking BMD and deferring screening for women with low BMD. Using BMD to assess breast cancer risk at age 65 prior to screening mammography is more cost effective than screening all women through age 79. ❖

Kerlikowske K, et al. JAMA 1999;282: 2156-2163.

Fecal and Oral Shedding of *H. pylori*

Several important unresolved questions about *Helicobacter pylori*, the causative agent of almost all non-NSAID related ulcers and a likely cause of gastric cancer, remain unanswered. The path by which *H. pylori* leaves a host to enter the environment, the environmental location, method of human acquisition, and individual susceptibility to this organism are uncertain. This study was directed to learn, by using polymerase chain reaction (PCR) testing, the frequency of *H. pylori* in saliva, stool, and vomitus of infected volunteers. Immunomagnetic separation (IMS)-PCR was chosen as the detection method because of its superior ability to identify live organisms.

After sodium phosphate-induced catharsis, ipecac-induced emesis, and volitional saliva expectoration, *H. pylori* detection by IMS-PCR was performed (n = 16).

Stool culture obtained prior to catharsis was culture negative in all 16 patients, but positive in 5/16 using IMS-PCR. Post-cathartic stools were *H. pylori*-positive in 11/16 subjects by IMS-PCR, but only 50% of specimens were culture-positive. All vomitus samples from infected person were culture-positive as well as IMS-PCR positive. Saliva was culture-positive in only 18.8% of subjects but IMS-PCR positive in 43.8%.

Despite the ready retrieval of *H. pylori* from saliva, there is little evidence of oral-oral transmission (e.g., the *H. pylori* strain present in married couples is rarely concordant and, thus far, studies of treated patients, whose infected partners are not treated, do not show significant risk of reinfection).

Saliva, stool, and vomitus all harbor *H. pylori*, which might serve as sources of transmission. Since up to half of middle-aged adults have been infected, the question might best be reframed to seek how the other half remain uninfected. ❖

Parsonnet J, et al. JAMA 1999;282: 2240-2245.

Allergic Asthma with Monoclonal Anti-IgE Antibody

Allergic mechanisms, dominantly mediated through IgE activation, are responsible for a significant burden of symptomatic asthma. After infusion of a binding antibody specifically directed against IgE (anti-E), serum-free IgE levels are dramatically lowered. This study evaluated the effect of 13 intravenous doses of anti-E over 20 weeks on asthma. Effect was measured on asthma symptoms, pulmonary function tests, use of inhaled beta agonists, and use of steroids.

The late phase reaction of asthma, beginning 2-8 hours after antigen exposure, has been linked to asthmatic inflammation and the long-term consequences of bronchial hyperreactivity, which correlate with asthma severity. Interruption of IgE affinity for target cells, or decreases in levels of activated IgE should reduce the late phase reaction intensity and its consequences.

Asthma symptom scores were significantly decreased by anti-E, as well as use of inhaled beta-agonist among recipients of high-dose IgE. Steroid use (inhaled and systemic) was able to be successfully reduced in patients who received anti-E. Peak expiratory flow rates were significantly improved at 20 weeks. Modulation of IgE activity through use of specific antibody may prove to be a useful therapeutic tool. ❖

Milgrom H, et al. N Engl J Med 1999; 341:1966-1973.

In Future Issues:

Using the Berlin Questionnaire to Identify Patients at Risk for the Sleep Apnea Syndrome